

### **Remarks**

Claims 1-29, 31, 35-38, 40-45 and 47-74 were pending in this application. The final Office action rejected claims 1-29, 31, 35-38, 40-45 and 47-74, and withdrew claims 50-74 from consideration. Applicant has canceled claims 48 and 50-74, leaving claims 1-29, 31, 35-38, 40-45 and 47, and 49 for consideration. Those remaining claims have been rejected as obvious under 35 U.S.C. § 103 in view of a variety of references. The obviousness rejection should be withdrawn because the Office action has improperly applied the standards of inherency, reversed the burden of proof for establishing an obviousness rejection, relied upon the Applicants' own specification for the disclosure of advantages to make allegations of obviousness, and disregarded claim limitations and evidence of unexpectedly superior results.

Several of the claims have been amended to address rejections made under 35 U.S.C. § 112. These amendments do not raise new issues after final rejection, but clarify claim language as requested by the examiner and simplify issues for appeal. In addition, several claims have been amended to correct minor typographical errors.

### ***Elections/Restrictions***

The Office action has withdrawn claims 50-74 from consideration because Applicants allegedly elected another group of claims by original presentation. Although Applicants disagree with this assertion, claims 50-74 have been cancelled to simplify issues after final rejection.

### ***Claim Rejections under 35 U.S.C. § 112***

Claim 48 was rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. That claim has been cancelled thereby rendering the rejection moot.

Claims 4, 6, 20, 21, 31 and 48 were rejected under 35 U.S.C. 112, second paragraph.

In claim 4, the phrase "detectable tracer is selected to interact with the test strip to slow migration" was said to be vague and clarification was requested. In particular, the Office action asked how the tracer interacts with the test strip. This interaction was explained (with respect to claim 49) in Applicant's prior response at pages 16-17. That explanation appears in the footnote

below for the examiner's convenience.<sup>1</sup> Since the language of claim 49 was considered to satisfy § 112 in view of the prior explanation of this term, claim 4 is believed to also satisfy § 112.

Claim 6 was said to be vague and indefinite because it allegedly contradicts claim 1 from which it depends. Claim 6 recites that "the detectable tracer is positioned beneath the surface of the test strip on which the liquid sample is placed." This language is said to contradict independent claim 1 in which the detectable tracer is distal to the application area, because the Office action interpreted the language to require that the tracer be placed immediately under the sample application area. However the claim language does not require that the detectable tracer be immediately beneath the sample application area, but rather only that the tracer be below a *surface* to which the sample is applied. That *surface* extends beyond the immediate area to which the sample is applied. As shown in FIG. 1 and the accompanying text at page 18, lines 6-7 and 16-20, the placement of the tracer deeper in the test strip permits the analyte to migrate more quickly along the strip to reach the primary capture line before the more deeply placed tracer, which encounters more resistance. Applicants submit that the language of claim 6 would be interpreted in view of the disclosure in the specification, and the limitations of independent claim 1, to be that the sample is applied upstream from the tracer which is placed deep in the strip to slow the movement of the tracer through the strip.

Claims 20 and 21 were rejected as being unclear. Applicants have amended the claims to clarify the language, as requested by the examiner.

Claim 31 has been amended to insert the language requested by the examiner to make the claim body correlate with the preamble.

Claim 48 has been cancelled thereby rendering the § 112 rejection moot with respect to that claim.

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<sup>1</sup> "For example, claim 49 calls for the detectable tracer to "interact with the test strip." The specification provides numerous examples of how the tracer "interacts with the test strip" to slow movement of the tracer along the path of liquid flow. Page 20, lines 26-31, states that the interaction can be achieved with a very large conjugate molecule (such as bovine serum albumin) that moves slowly through the test strip. Other examples that are given at page 21, lines 1-5, include the size, polarity or charge of the A-L-T conjugate. Page 21, lines 6-10, provides examples of specific sizes of colloidal gold particles that can be selected "depending on the migration characteristics desired." Page 24, lines 26-31, describes delayed-release reversible immobilization using co-molecules such as sucrose, mannitol, glycerol, PVA or PVP. The embodiment of FIG. 2 described on pages 17-18 is entitled "A-L-T Conjugate Mobilization Zone Under Sample Pad," and it describes a test strip in which the conjugate tracer is present deep in the test strip, such that the superficially applied sample encounters less resistance than the conjugate tracer. This difference allows the sample to interact with the test strip in a way that it migrates through the pad more quickly than the subjacent conjugate migrates (page 18, lines 16-20)."

***Rejections Under 35 U.S.C. § 103***

*Claims 1, 3-5, 10-13, 20, 21, 31, 35, 36, 40, 41, 45 and 49*

Claims 1, 3-5, 10-13, 20, 21, 31, 35, 36, 40, 41, 45 and 49 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Boehringer et al. (WO 98/39657). The Office action notes that Boehringer et al. differs from the claimed invention in that it fails to disclose that the detectable tracer migrates through the test strip more slowly than the analyte, so that the analyte reaches the primary capture zone before the detectable tracer. However the Office action states that the microspheres of Boehringer et al. are larger than the particles disclosed in the specification, and are coated with BSA, such that one of ordinary skill in the art would recognize that the detectable tracer migrates more slowly than the analyte. In other words, the invention is said to be inherent in the disclosure of Boehringer et al.

The standard for establishing a §102/103 rejection based on inherency is set forth in MPEP 2112:

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (reversed rejection because inherency was based on what would result due to optimization of conditions, not what was necessarily present in the prior art); *In re Oelrich*, 666 F.2d 578, 581-82, 212 USPQ 323, 326 (CCPA 1981). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

The rejection of the claims in view of the alleged inherent disclosure of Boehringer et al. is improper because Applicants have already shown that Boehringer et al. does not *necessarily* disclose an assay in which sequential migration of the analyte and tracer occurs. As explained in Applicants' specification at page 21 (and at page 19 of Applicants' prior response), sequential migration of the analyte and tracer is the result of a specific combination of tracer complexes, pore size, binding partners and other factors that permit separation of the wave fronts in which the analyte and tracer migrate. As proven in the Declaration of Buck submitted with Applicants' prior response, it is quite possible for the detectable tracer and analyte to reach the primary capture zone together,

for example if the detectable tracer does not migrate a distance sufficient for separation of the wave fronts to occur. This fact alone illustrates that the Office action has not established a prima facie case of obviousness, because the cited reference does not *necessarily* satisfy the claim limitation that “the detectable tracer is present on the test strip in a position that a distal flow of analyte reaches the primary capture area before the distal flow of tracer reaches the primary capture area.”

The Office action discounted the Declaration evidence because a separation distance between the labeling zone and the capture zone is not recited in the claims. Such a position ignores the fact that the burden of proof is on the PTO to show that assay disclosed in the Boehringer et al. reference *necessarily* achieves the separation of the wave fronts that allows the analyte to reach the primary capture zone first. Applicants have demonstrated that the Office action is incorrect in asserting that this *necessarily* occurs. A prima facie case of obviousness has not been made. Since the asserted basis of the rejection is defective (that the cited reference necessarily shows sequential migration of the analyte and then the detectable tracer), the rejection must be withdrawn. In any event, the claim does include the limitation that the “detectable tracer is present on the test strip *in a position* that a distal flow of analyte reaches the primary capture zone before a distal flow of tracer reaches the primary capture area.” The claimed placement of the detectable tracer in such *a position* would also clearly include a separation distance, even though a separation distance is not specifically claimed.

Moreover, the disclosure of Boehringer et al. itself repeatedly demonstrates that the reference did not disclose a test strip in which the analyte reaches the primary capture zone first to occupy the immobilized binding partner, as presently claimed. The claimed invention calls for a test strip in which the analyte occupies the binding partners in the primary capture zone before the detectable tracer reaches them so that the detectable tracers pass through the primary capture zone. In contrast, Boehringer et al. repeatedly refers to a system in which the sample and labeled analyte analog flow to and through the capture zone together so that they *compete* for binding to the immobilized binding partner. See Boehringer et al. at page 16, lines 27-31.<sup>2</sup> The only way the Boehringer et

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<sup>2</sup> “Sample and labeled analyte analog flow to and through the capture zones and compete for binding to the immobilized first sbp member.”

al. assay is described is that the labeled antigen competes with sample antigen for antibody immobilized in the barrier zone. Boehringer et al. at page 18, lines 30-32. Hence Boehringer et al. describes the prior art problem that Applicants' currently claimed invention was designed to overcome, namely the loss of sensitivity caused by the competitive instead of sequential interaction of the analyte and labeled tracer in the primary capture zone. As disclosed in Applicants' specification, and further demonstrated in the Declaration of Buck, the sequential migration in the claimed invention avoids the loss of sensitivity of the merely competitive assay of Boehringer et al.

The Office action also does not establish a prima facie case of obviousness with respect to many of the other rejected claims. Claim 3 calls for the tracer to be heavier than the analyte, and there is no discussion in the Office action or Boehringer et al. reference about relative weights of the tracer and analyte. Claim 4 calls for the tracer to be selected to interact with the test strip to slow its migration relative to the analyte; again the references are silent about such selection criteria because the references do not even appreciate the problem being solved, much less suggest the claimed solution. Claim 5 concerns relative sizes of the tracer and analyte, and their relation to the bibulous strip, a subject on which the references and Office action are also silent.

One recurrent theme of the Section 103 rejection is that it assumes that Boehringer et al. discloses sequential migration of the analyte and then the detectable tracer (it does not), and then uses that speculative "teaching" to allege other claims are obviousness. Speculation about optimized conditions in Boehringer et al. can not be the basis of an obviousness rejection, as noted by the Federal Circuit's decision *In re Rijckaert*, 28 USPQ2d 1955 (Fed. Cir. 1993).

#### *Claims 2, 6 and 7*

Claims 2, 6 and 7 were rejected under § 103 as unpatentable over Boehringer et al. in view of Fredrickson, which was said to teach a tracer beneath the surface of the test strip. Fredrickson discloses a conjugate pad 3 impregnated with a diffusible binding partner for the analyte of interest. See column 3, lines 44-47. The binding partner is disclosed at column 3, lines 47-49 to be a labeled antibody. The Frederickson assay is

performed by the test sample migrating into the conjugate pad 3 and binding the labeled antibody as the analyte and antibody continue their migration *bound together*. Hence Fredrickson discloses the submerged conjugate pad helps mix the analyte and conjugate together to facilitate their simultaneous movement through the test strip.

The teaching of Fredrickson is the antithesis of the present invention, in that it teaches the use of the submerged conjugate to achieve *conjoined movement* of the analyte and conjugate, whereas the claimed invention specifically requires that the detectable tracer is positioned within the test strip in a position that the distal flow of tracer reaches the primary capture area after the distal flow of analyte. To the extent that Frederickson suggests the submerged conjugate achieves the opposite of the claimed invention, the claimed invention can not be said to be obvious in view of Fredrickson.

Moreover, the Office action has alleged that Boehringer et al. teaches the separation of the tracer and analyte. If the Office action persists in that view, contrary to the Declaration evidence and explicit teaching of Boehringer et al., then it must at least be acknowledged that it would not be obvious to combine Fredrickson with Boehringer et al., because such a combination would be based on a teaching (simultaneous flow of the analyte bound to the conjugate) which would defeat and frustrate the alleged purpose of the primary reference (sequential flow of the analyte and the conjugate).

Finally, even if the combination were made it would not establish a *prima facie* case of obviousness with respect to a submerged detectable tracer comprising an analyte analog (as in claim 12), an analyte or analog (as in claims 14, 22). Fredrickson does not disclose a submerged analyte or analyte analog; it only discloses a submerged labeled antibody. It can not be said to disclose or suggest a submerged analyte analog, and a *prima facie* case of obviousness with respect to that feature has not been made.

#### *Claims 7 and 14*

Claims 7 and 14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over the combination of Boehringer et al. and Leuving (U.S. Patent No. 4,313,734). Claim 7 states that the “tracer is selected based on its polarity or charge to provide specific migration characteristics that retard migration of the tracer relative to migration of the analyte.” Claim 14 states that the detectable tracer “comprises a visually

detectable label covalently attached to analyte of analyte analog.” The Office action alleges that it would have been obvious to use the labels of Leuving for the methods of Boehringer, because Boehringer et al. states that the Leuving labels are suitable for use with the Boehringer et al. device.

A prima facie case of obviousness has not been made with respect to claim 7 because the Office action has disregarded the claim limitation that the tracer is selected based on its polarity and charge to provide specific migration characteristics that retard migration of the tracer relative to migration of the analyte. The cited references are completely silent about selecting such a particle based on its interaction with the test strip to retard its migration. The only reference to charged particles in Leuving at column 3 is for the purpose conferring attraction or repulsion of the particles *for each other*, for example to achieve aggregation or flocculation of the particles with one another. The references are completely silent about taking interaction with the substrate into account to retard the flow of the tracer (note claim 7 depends from claim 4 that requires this interaction with the test strip). Since none of the cited references disclose or suggest that the polarity or charge be selected based on an interaction with the test strip, a prima facie case of obviousness has not been made.

The invention of claim 7 would not be produced by the alleged combination of references, because none of the references disclose that the characteristics of the test strip be considered along with a polarity of charge of the test strip. If one blindly selected charged particles as proposed by the Office action, many of those blind selections could *increase* the rate of migration of the tracer through the test strip, instead of retarding it as claimed. For example, selecting particles with similar charges could inhibit aggregation of particles that could reduce their effective size and increase their migration through the substrate. The selection of the claimed species of interactions (that retard migration of the tracer) is not disclosed in the cited references. The Office action can not use applicant’s own teaching that migration be slowed to make the selection allegedly obvious. Moreover, since there is no teaching in Boehringer et al. that the migration of the tracer be slowed, that reference can not be relied upon to supply the missing element of the claim. Even if Boehringer et al. had inherently disclosed a possible embodiment in which the tracer migrated more slowly than the analyte, the total absence of teaching in

Boehringer et al. about slowing the rate of migration of the tracer would prevent it from being used in any combination of references that would implement a goal that was never disclosed or even recognized by that reference.

Claim 14 calls for the detectable label to be covalently attached to an analyte or analyte analog. The Office action contends that covalent bonding of labels is disclosed in Leuving. Although the Office action does not cite a particular passage in this patent, it is believed it refers to column 2, lines 56-59: "Under coupling is understood any chemical or physical binding, such as binding via covalent bonds via hydrogen bridges, polar attraction and adsorption." Hence the cited reference provides a rote list of different modes of attachment which are considered equivalent. A *prima facie* case of obviousness is not established by citing to a long list of species and contending that it would be obvious to select a particular species from the list of possibilities. To establish a *prima facie* case of obviousness, the rejection must provide a reason why one skilled in the art would have selected *covalent* bonding from the list of possible modes of attachment (covalent bonds, hydrogen bridges, polar attraction, adsorption). There is no such teaching in the references, and the rejection of claims to covalent bonding is mere hindsight reconstruction of the claimed invention based on the Applicants' own disclosure. Since a *prima facie* case of obviousness has not been made with respect to this claim, the § 103(a) rejection of claim 14 should be withdrawn.

Even if a *prima facie* case of obviousness had been established with respect to claim 14, it would have been rebutted by evidence of unexpectedly superior results. As noted in the Declaration of Buck at paragraph 5, the covalent bonding has been found to avoid separation of the tracer from the analyte or analog that allows the analyte or analog to act a "free analyte" that falsely elevates test results. The Office action and the cited references are devoid of any disclosure or suggestion that this greater specificity could be achieved by covalently bonding the label to an analyte or analyte analog, as in claim 14. In the face of this evidence of unexpected superiority, claim 14 should be allowed.

#### *Claims 8 and 9*

Claims 8 and 9 were said to be obvious in view of the combination of Boehringer et al. and Leuving with the Terminiello et al. reference. In particular, Terminiello et al. was said to



disclose addition of PVP and other additives to a membrane. The Office action alleged it would be obvious to treat the modified device of Boehringer et al. with PVP as taught by Terminiello et al. because Terminiello et al. shows that such conditioning of the membrane provides advantages by reducing void spaces within the matrix of the membrane and promoting absorption of the fluid fraction of a biological sample.

Claims 8 and 9 depend from claim 7, which is allowable for the reasons already noted. In addition, the rejection relies on hindsight reconstruction of the claimed invention in view of the Applicants' own disclosure. Terminiello et al. discloses a list of conditioning agents at column 13, lines 1-4, one of which is PVP. The Office action contends it would be obvious to select a particular species within that genus of agents, and incorporate it into the test strip of claim 8 and 9. A prima face case of obviousness is not established by arbitrarily picking and choosing particular species within a genus. To establish obviousness it must be shown why one skilled in the art would have selected PVP from the long list of agents (such as protein, glucose, dextrin, dextrans, starch, polyethylene glycol, and PVP) listed in the patent. The allegation that a particular species from the list would be obvious to use in combination with the other references is mere hindsight reconstruction of the invention from individual elements that appear in the prior art.

Obviousness requires more than the ex post facto justifications set forth in the Office action. In fact, there is no motivation in the prior art for choosing PVP from among this list of agents, and a prima facie case of obviousness has not been established with respect to these claims.

*Claims 22-24, 26 and 29*

Claims 22-24, 26 and 29 were rejected in view of a combination of Boehringer et al. and Leuving. The Office action contends that the references show particles that are the same size as used by the Applicants, such that one of ordinary skill in the art would recognize that the rate of migration for the labeled analyte analog would be slower than the rate of migration of the analyte such that the analyte would reach the primary capture area before the detectable tracer. Applicants disagree and request reconsideration.

The mere similarity in size of particles attached to the analyte analog does not establish a prima facie case of obviousness. As already noted in this response, and taught in Applicants'

specification at page 21, lines 13-22, the rate of migration depends on a relationship between the substrate and the particles. Mere similarity of particle size implies nothing about migration rates in the absence of a consideration of the substrate with which the particle interacts. Hence the stated rationale for the rejection is incomplete, and does not establish a prima face case of obviousness.

The rejection also assumes that there is some teaching in the prior art that sequential migration of the analyte and tracer occurs. Although the Office action contends that sequential migration occurs in Boehringer et al. this response has already shown that the *potential* for this *possibly* happening in Boehringer et al. is legally insufficient to reject the claims. In any event, such an allegation is contrary to the actual statements in Boehringer et al. that the analyte and labeled tracer flow together down the strip to the capture zone where they compete with one another (page 16, lines 10-15 and 28-33). The theory of operation of Boehringer et al. is set forth at page 16, lines 36-38 as being that the labeled analyte analog “*competes* effectively for binding at the downstream capture.” This differs from the claimed sequential migration of claim 22 in which the “flow of analyte reaches the primary capture area before the tracer such that subsequent binding of tracer to the first antibody is inhibited and unbound tracer continues along the path of flow to the second antibody to provide a signal....” This sequential migration (in which the analyte occupies the capture zone before the detectable tracer even reaches it) differs from the stated operation of Boehringer in which the analyte and analog are simultaneously competing for binding, and the analog binds only after the analyte has been depleted. This simultaneous binding of analyte and analyte analog-tracer in Boehringer et al. represents the problem that Applicants’ method overcame, because such simultaneous competitive binding was found to reduce sensitivity of the tests. The assertion that Boehringer et al. inherently discloses the claimed method can not be supported when such an “inherent” teaching directly contradicts the method as described in the Boehringer et al. specification.

Claims 23 is allowable for reasons already set forth in connection with other claims directed to covalent linking of an analyte or analog to the detectable label.

Claims 24 specifically notes that the tracer is selected so that a diameter of the tracer is small enough to migrate through the bibulous test strip but not so large that it is trapped by pores of the bibulous strip. The Office action does not cite any disclosure in the cited references that the diameter of the tracer have these characteristics with respect to the test strip, and a prima

facie case of obviousness has not been made with respect to this claim. The prior art is devoid of any suggestion that consideration be given to the relationship of the test strip and tracer.

Other rejected claims depend from claims that are allowable for the reasons set forth above. These claims are also allowable because of the structure and method steps set forth in those claims.

### **Terminal Disclaimer**

The Office action states that the claims of the pending application are rejected under the judicially created doctrine of obviousness-type double patenting, because “it would have been obvious that the claims [of] U.S. Patent No. 6,699,722 would encompass the claims of 1-38 of application 10/686,548.” The claims of the ‘722 patent concern a test strip in which the “detectable tracer has a weight greater than a weight of the analyte.” Applicants submit it is not accurate to assert that these claims from the ‘722 patent would have encompassed the claims of the pending application. There are many embodiments encompassed by the pending claims in which the tracer does not have a weight greater than the analyte. For example, difference in size, polarity or other chemical interaction with the substrate can achieve the unique differential migration of the claims without a weight difference.

Once allowable subject matter is identified in the present application, Applicants will consider whether to submit a terminal disclaimer.

### **Summary**

The Office action has not established a prima facie case of obviousness of the pending claims. The assertion that Boehringer et al. inherently discloses sequential migration of the analyte and detectable tracer has been disproven by the Declaration of Buck which showed that it is certainly possible that the analyte and detectable tracer reach the primary capture area together instead of sequentially as claimed. Since the claimed device is not *necessarily* disclosed in Boehringer et al., the rejection based on inherent obviousness must be withdrawn. Moreover, the assertion that sequential migration occurs is contrary to Boehringer’s “competitive format” (page 16, line 8) description of his method in which simultaneous competition of the analyte and tracer occurs. This is different from the claimed invention in which analyte reaches the primary capture area first to occupy the binding sites before the tracer reaches the primary capture area.

The assertion in the Office action that the Declaration evidence is unconvincing because the claims do not recite a separation distance between the sample application and primary capture zones in inapposite, because it inverts the burden of proof. It is the burden of the USPTO to establish a prima face case of obviousness by explaining why the assay disclosed in Boehringer et al. *necessarily* discloses the claimed invention. The Declaration of Buck has shown that this burden has not been met, and the rejection has therefore been overcome. In any event, the claims do recite that the “detectable tracer is present on the test strip in a position that a distal flow of analyte reaches the primary capture area before a distal flow of tracer.” This claim language would clearly include positioning the tracer and primary capture area a sufficient distance that separation of the wave fronts of the tracer and analyte can occur.

For these and the other reasons set forth above the claims are allowable, and a Notice of Allowance should issue. If any matters remain for resolution prior to issuance of the Notice of Allowance, the examiner is invited to telephone the undersigned at the telephone number shown below.

Respectfully submitted,

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